

### The Invention

The invention relates to controlled release dosage form of azithromycin. The term "controlled release" is defined as being generic to both sustained release and to delayed release dosage forms. For example See Applicants' specification at page 7, lines 20-27 where it is stated:

"For the purpose of this application, various embodiments of "controlled release dosage forms of azithromycin" have been described as "sustained release" embodiments or "delayed release" embodiments, for ease of description. Without intending to be limiting, sustained release dosage forms of azithromycin are those which slowly release azithromycin. Delayed release dosage forms of azithromycin are those which release little or no azithromycin for a predetermined time, then release azithromycin quickly or in a sustained fashion."

### The Rejection

Claims 149 and 150 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Curatolo et al. (US Pat. No. 5,605,889). The Examiner stated, in pertinent part:

Curatolo teaches a dosage form of azithromycin which can be administered to a mammal. The goal of Curatolo's dosage form is to address "food effect", i.e., the presence of food in the gastrointestinal tract adversely affecting the residence time of a therapeutic agent by not allowing sufficient absorption into the bloodstream. The dosage form can be in the form of a tablet, including both swallowable-only and chewable form (col. 2, lines 49-51). The azithromycin dosage forms as taught by Curatolo can provide azithromycin ready for dissolution in the gastrointestinal tract immediately following ingestion or they disintegrate rapidly following ingestion. It is believed that if the azithromycin dosage form provides azithromycin within a certain time period following ingestion, the azithromycin will be absorbed into the bloodstream at a rate which results in substantially no food effect. At least about 90% of the azithromycin dissolves within about 30 minutes of ingestion (col. 5, lines 6-24). The tablets can include a variety of ingredients including disintegrants, binders, lubricants, etc. (see col. 6-col. 7).

It is understood by the examiner that the dosage form as taught by Curatolo is controlled (delivering an amount of azithromycin in a time period), and that, because dissolution occurs in the gastrointestinal tract, which can include the mouth and stomach, dissolution occurs distal to the duodenum. [Pages 2-3 of the Office Action].

Claims 149, 150, 164, 173-175, and 208-212 stand rejected under 35 USC 103(a) as being unpatentable over Curatolo et al. (US Pat. No. 5,605,889) further in view of Urquhart et al. (US Pat. No. 4,4234,153). The Examiner stated, in pertinent part:

As stated above, Curatolo teaches a controlled dosage form that delivers azithromycin to the gastrointestinal tract. However, Curatolo does not teach a matrix for delivery of such dosage form.

Urquhart relates to a drug delivery system. Urquhart has as its object the delivery of a drug reservoir that releases drug in the stomach for absorption in the stomach. It is taught that if a delivery system is made available that remains in the stomach for releasing drug at a controlled rate for achieving therapeutic blood levels, such a delivery system would be clinically useful in the practice of medicine (col. 2, lines 9-25). The model is a drug delivery device housing a multiplicity of tiny pills for the controlled delivery of drug over time. The tiny pills comprise a core of drug surrounded by a wall formed a rate-releasing controlling material (col. 3, lines 48-55). The delivery device can be made with a reservoir. The reservoir is formed from hydrogels that exhibit the ability to swell in water and retain such water in its structure. Suitable materials for the hydrogel include cellulose gum or gelatin (col. 4, lines 10-32). The wall surrounding the drug can be made of fatty ester mixed with a wax (col. 4, lines 46-50). Examples of suitable drugs that may be contained in the delivery device include erythromycin and the like (col. 6, lines 20-21).

Motivation to utilize the delivery design of Urquhart for the dosage form of Curatolo would have arisen because Urquhart's delivery design releases drug into the stomach of the gastrointestinal tract, thereby allowing absorption into the bloodstream. Such absorption would allow therapeutic blood levels to be reached, thus addressing the risks of "food effect". [Pages 3-4 of the Office Action]

#### Applicants' Traversal

Applicants traverse the rejection of claims 149 and 150 over Curatolo on the basis that Curatolo is not addressed to and does not disclose controlled release dosage forms. Curatolo in fact teaches immediate and/or fast release and, accordingly, teaches away from the instant invention.

Curatolo is grounded in the determination that certain dosage forms which release azithromycin quickly for dissolution avoid adverse food effects. Quick and/or immediate release and dissolution are therefore important features for the dosage forms disclosed in Curatolo. See, for example, the following quotations from Curatolo:

The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus,....it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention. [Curatolo, column 4, lines 30-35]

See also the following quotation:

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions) or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. [column 5, lines 7-13]

Clearly, a touchstone of Curatolo is fast disintegration and/or fast dissolution to provide azithromycin in the GI tract as soon as possible. There are no embodiments disclosed in Curatolo in which a dosage form is deliberately engineered in order to slow down azithromycin release. Slow (sustained and/or delayed) release is simply not a factor which is useful in Curatolo's no food effect dosage forms. Rather, quick and/or immediate release is an important factor in Curatolo, i.e., essentially the opposite of what the inventors are seeking to achieve in the instant invention, focused as they are on different problems. Thus one skilled in the art who was interested in achieving azithromycin controlled release, i.e., sustained or delayed release, would dismiss Curatolo out of hand as irrelevant. Because Curatolo teaches away from the instant invention, the instant invention cannot be obvious over Curatolo. Withdrawal of the obviousness invention over Curatolo is accordingly respectfully requested.

The rejection of claims 149, 150, 164, 173-175, and 208-212 over Curatolo in view of Urquhart is traversed on similar grounds, it being further urged that the references are not properly combinable because they are directed to different purposes. Applicants' arguments against Curatolo from above are incorporated by reference in this regard. Again, a rejection over references which include Curatolo is not tenable because Curatolo is directed to immediate release dosage forms, not sustained and/or delayed release as is the instant invention. Similarly, Urquhart is directed toward controlled release as well, specifically a hydrogel matrix system that that is retained in the GI tract and which contains a drug that is essentially metered out over time. A rejection which combines the teachings of controlled release (Urquhart) and immediate release (Curatolo) is simply not tenable. Urquhart was cited for its teaching of a matrix system, a system which is well known to those skilled in the art as useful in making controlled release devices. It is not tenable to combine the matrix teachings of Urquhart into the immediate release teachings of Curatolo because to do so would defeat the purpose of Curatolo, i.e., Curatolo does not teach matrix systems in the first place because he is not interested in controlled release.

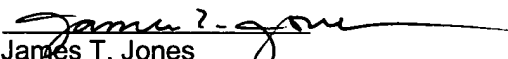
In different words, the Examiner has based the rejection on two different references, but the combination of references is improper unless the prior art suggests the combination, which is not the case here, where the teachings are completely different. See In re Bond, 15

Uspq2d 1566 (Fed. Cir. 1990) in which it was held that the PTO erred in rejecting a claimed invention as an obvious combination of the teachings of two prior art references when the prior art provided no teaching, suggestion, or incentive supporting the combination. See also Smithkline Diagnostics v. Helena Laboratories Corp., 8 USPQ2d 1468, where the court stated that a challenger to the validity of a patent "cannot pick and choose among the individual teachings of assorted prior art references to recreate the claimed invention"; the challenger has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. See also In re Mahurkar Patent Litigation, 28 USPQ2d 1801 (N.D. Ill. 1993) where it was stated that decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention is a forbidden *ex post* analysis. Clearly, there is no suggestion as between Curatolo and Urquhart to make the combination of teachings used to fashion the rejection. It is accordingly respectfully requested that the rejection be withdrawn.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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